Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Biomedical Engineering

Electrospun biomedical nanofibers and their future as intelligent biomaterials

Ishaq Lugoloobi[1,2], Wang Yuanhao[1], Ifra Marriam[3], Jinming Hu[2], Mike Tebyetekerwa[4] and Seeram Ramakrishna[5]

Abstract

Electrospinning is one of the most studied techniques for the facile, versatile, and scalable synthesis of nano/micro/macro-fibers. The process employs various polymers of natural and synthetic origin for the preparation of fibers with several immeasurable designs, in virgin and composite forms. Bestowed with alluring properties such as solubility/solvolysis, biocompatibility, and degradability, electrospun fibers have found numerous applications as biomedical materials for tissue engineering, localized therapy, wound dressing, and drug delivery. Their properties enable effortless and precise compounding with various biopharmaceuticals and nanomaterials that are sensitive to chemo-, magnetic-, and photo-cathartic modalities. We hence provide a summarized insight into the recent past and predict the future of electrospun nanofibers as intelligent systems for biomedical applications.

Addresses

[1] Hoffmann Institute of Advanced Materials, Shenzhen Polytechnic, 7098 Liuxian Boulevard, Nanshan District, Shenzhen 518055, PR China
[2] CAS Key Laboratory of Soft Matter Chemistry and School of Chemistry and Materials Science, University of Science and Technology of China, Hefei 230026, China
[3] School of Mechanical, Medical, and Process Engineering, Faculty of Engineering, Queensland University of Technology, 2 George Street, Brisbane, QLD 4000, Australia
[4] Dow Centre for Sustainable Engineering Innovation, School of Chemical Engineering, The University of Queensland, St Lucia, Brisbane, QLD 4072, Australia
[5] Centre for Nanofibres and Nanotechnology, National University of Singapore, Singapore, 117581, Singapore

Corresponding authors: Tebyetekerwa, Mike (m.tebyetekerwa@uq.edu.au); Yuanhao, Wang (wangyuanhao@szpt.edu.cn); Ramakrishna, Seeram (seeram@nus.edu.sg)

Current Opinion in Biomedical Engineering 2022, **24:**100418

This review comes from a themed issue on **Biomaterials: Intelligent Biomaterials**

Edited by **Seeram Ramakrishn**, **Ravin Narai**, **Himansu Sekhar Nanda**, **Masoud Mozafari** and **Gulden Camci-Unal**

Received 5 August 2022, revised 12 September 2022, accepted 14 September 2022

Available online xxx

https://doi.org/10.1016/j.cobme.2022.100418

2468-4511/

Keywords

Electrospinning, Nanofibers, Biomedical applications, Intelligent materials.

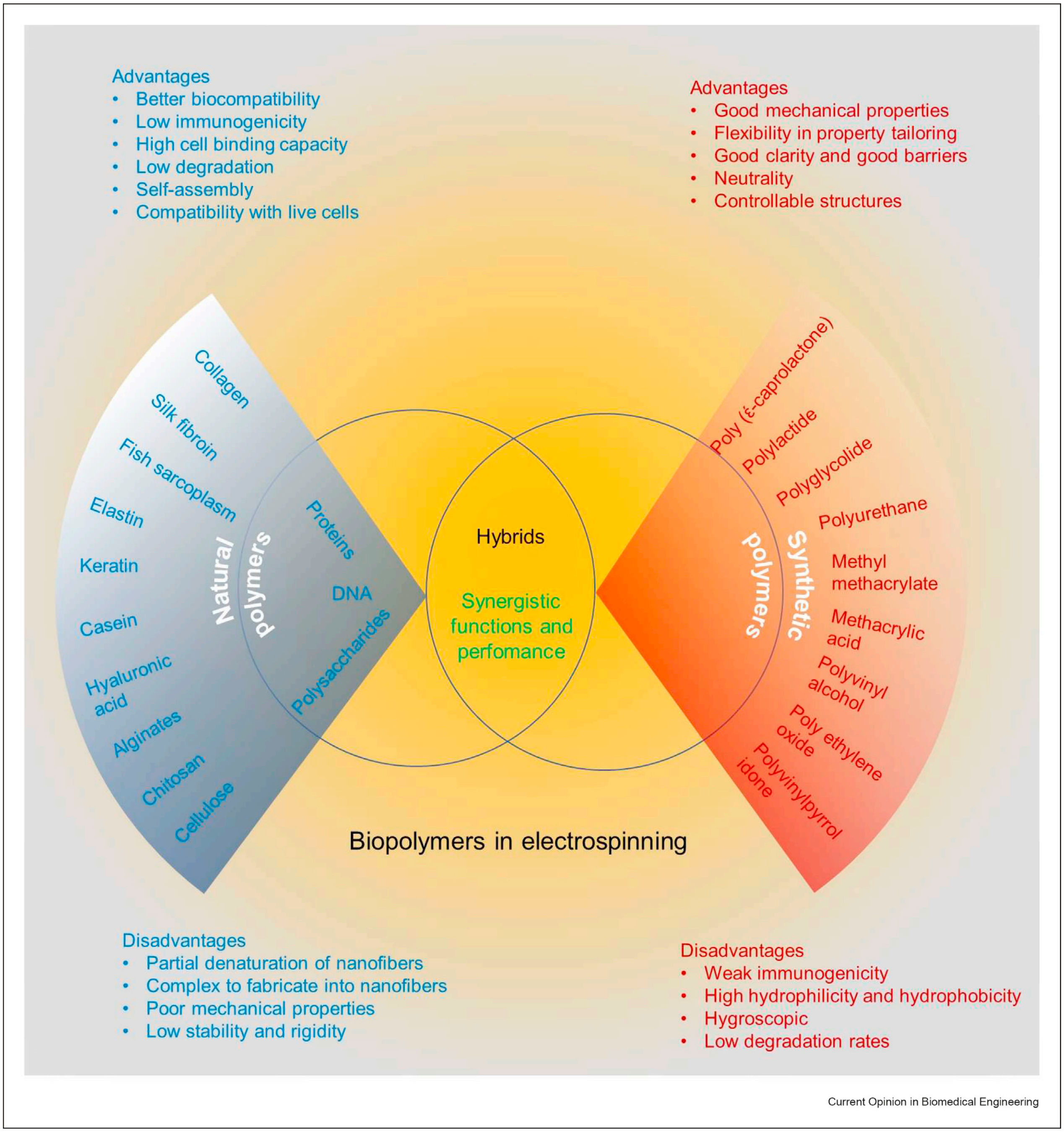
Introduction

Nanotechnology is a modern scientific approach that employs nanomaterials to seek solutions to various global challenges such as energy, clean water, health and medicine, climate, and many other scientific contests [1,2]. Electrospinning is one of the most studied techniques in nanotechnology, capable of concocting fibers with various dimensions and morphologies. It uses polymeric solutions and strong electric fields to spin nano to micro-sized continuous and non-continuous fibers, for a wide range of applications [3,4]. During electrospinning, nanomaterials can be tailored to possess useful physicochemical properties, including biocompatibility, non-toxicity, and environmental sensitivity, in various morphologies ranging from one-dimensional (1D) fibers, two-dimensional (2D) fiber films, three-dimensional (3D) fiber sponges and four-dimensional (4D) fiber-based printed objects [4]. Amongst these, 1D nanofibers are easily accessed and employable as the basic building blocks for 2D, 3D, and 4D fiber-based options. With electrospinning, special nanomaterials can also be added into and onto the fibers both *in-situ* or *ex-situ* in numerous designs owing to the technique's simplicity and relaxed control of its parameters. In cases employing biopolymers, the various obtained fibers tend to have improved and controllable surface area and dimension, high aspect ratio, morphology, shape, inter/intra fibrous porosity, and alignment. These properties are critically important for practical biomedical applications [5–7]. This brief insight therefore narrowly focuses on the electrospun bio nanofibers for application in health care and their prospect as intelligent biosystems.

Biopolymers utilized in electrospinning

Polymers are complex and versatile sets of organic materials constructed from simple units by polymerization. Currently, more than hundreds of polymers can be directly electrospun into nanofibers. The polymers used in electrospinning are broadly categorized into natural or synthetic (Figure 1). Synthetic polymers are currently more explored in electrospun drug-cargo nanofibers than their natural counterparts, owing to their qualitatively and quantitatively pleasing properties such as good

Figure 1



Advantages and disadvantages of the common electrospun biopolymers.

mechanical properties, flexibility in property tailoring, neutrality, and easily controllable structures. Though inherent weaknesses over the natural forms are still imminent such as weak immunogenicity, extreme hydrophilicity and hydrophobicity, and low degradation rates. Therefore, hybrid blends with both natural and synthetic polymers are the most optimum alternatives owed to their synergistic mechanical, chemical, and biological functioning with durability.

For natural polymers, the cardinal examples for bio nanofiber spinning include polysaccharides like cellulose, chitosan and alginate derivatives, and protein components like elastin, collagen, silk, and fish sarcoplasm. These natural polymers form nano to micrometer elongated fibers capable of fashioning chemical linkages and electrostatic bonds with live cells and charged molecules, respectively, *via* precise cell-binding protein sequences such as RGD (arginine/glycine/aspartic acid) and the

RGD containing peptide iRGD (internalized RGD) with a sequence (CRGDKGPDC), for delivery of drugs such as doxorubicin. Natural fibers can also form protective barriers by neutralizing gastric acid, thus enabling encapsulation of pH-sensitive live cells, molecules, and organisms. Nevertheless, they face numerous challenges such as being complex to spin into fibers, poor mechanical properties, low stability and rigidity, partial denaturation, *etc.* However, strenuous efforts involving co-polymer blending, hydrogen bond formation, and tweaking of the solution viscosity are currently exploited [5–7]. The blends particularly bestow supportive functions, for instance compositing hydrophilic chitosan and cellulose acetate with polyethylene oxide or polyvinyl alcohol ensures painless electrospinning [8]. While blending with fluoroalcohols particularly cracks the partial denaturation of natural polymers by depressing the denaturation temperature and the loss of the triple helical structure [9].

Functional agents including inorganic species, metal nanoparticles, biomolecules, and many others with appealing stability, solubility, and new functions can be incorporated as part of the viscous electrospinning dope. These agents are applicable *in-situ* within the spinning dope, during spinning, or *ex-situ* after spinning of nanofibers. The viscosity of the electrospinning solution, and the parameters from the process and environmental effect control the formation of electrospun fiber geometries. For example, (1) droplets spinning-electrospraying is generally formed at low viscoelasticity with high voltages, (2) beads-on-string/beads-thin filament connection, formed by partial stabilization of fibers owed to the entangled polymer networks, and (3) the uniform nanofibers, formed at higher viscosities after sufficient containment of the Rayleigh instability for fiber construction. Thus, there are various strategies for reshaping the electrospun fiber materials like working around with the applied voltage, the associated polymers, spinning dope engineering, and fiber collection geometry. Precise control of these regimes not only ascertains the fiber formation process but also broadens the various polymer and additive types/blends exploited, thus influencing chemical composition, and utilization of numerous effortless, cheap, and green solvents such as water, methanol, ethanol, and methyl acetate. This allows market extension and projection towards advanced fibers for smart and intelligent biosystems.

For post-electrospinning modification processes aiming at tuning the mechanical properties and enhancement of the surface hydrophilicity and bioactivity, plasma treatment can be employed. This typically involves inert Ar and N_2 gases and air, applied to purge nanofiber surface contaminants before the installment of polar groups or encampment of proteins and non-polymeric biomolecules. The precise treatments also improve; surface reactivity and surface energy, mechanical functionality, biosafety, cell–biomaterial interaction including propagation for tissue restoration, the desirable cellular responses, absorption of cancerous and other pathogenic cells, and allows continuous biological activity and controlled drug load and release. Notably, the plasma treatment process is fast and time-saving, limited to surface concentrated effects, solvent-free, enables surface functionalization using various gases, and thereafter immobilization of different components of the extracellular matrix during use. However, its superficial usage limits internal fiber functionalization, though this can be resolved by combining the process with the wet chemical method.

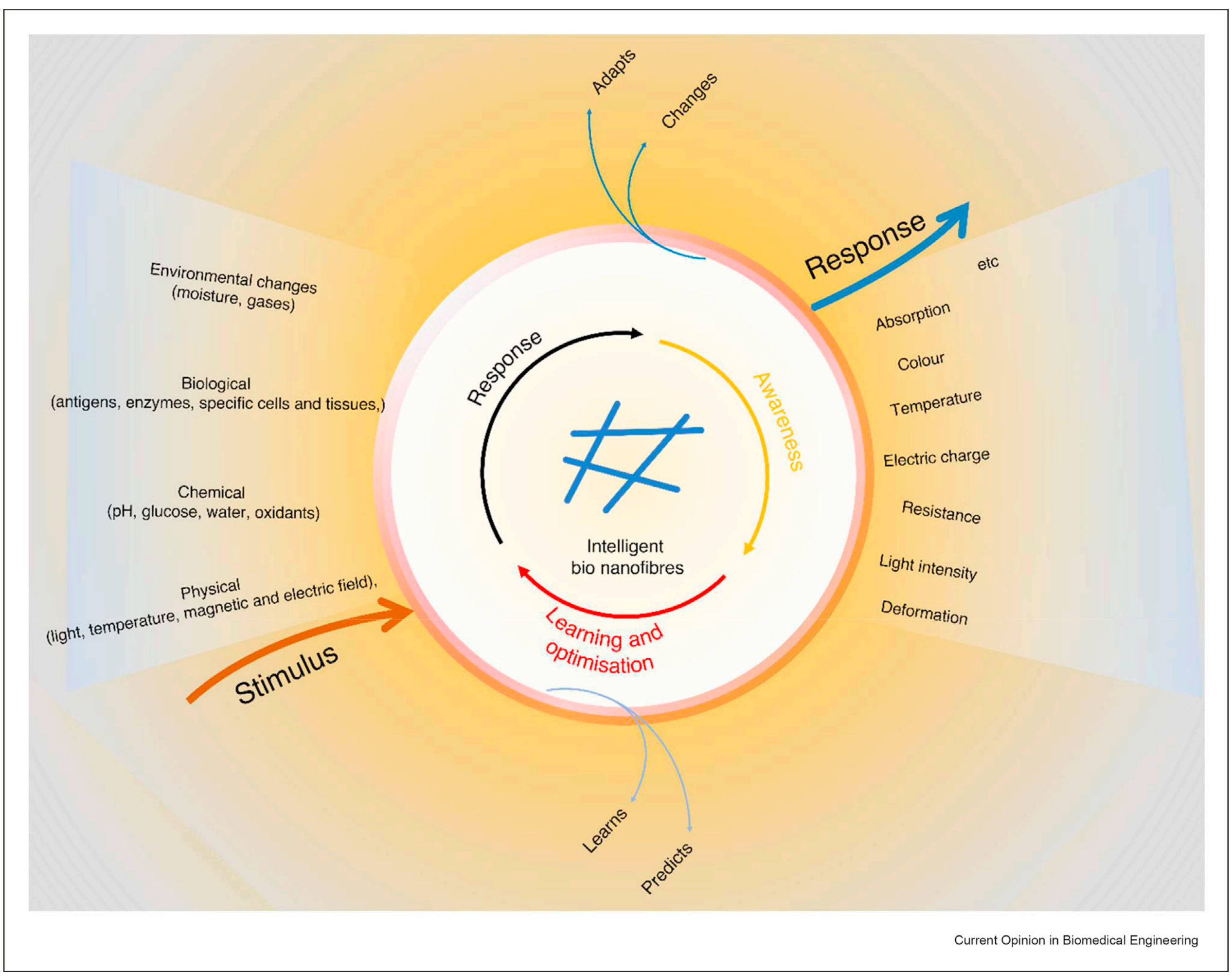
Surface graft polymerization, peptide grafting, co-electrospinning, layering technique, and chemical immobilization are the other currently existing electrospun fiber modification processes in need of further improvement, probably *via* green synthesis, precise control of the engineering parameters, utilization of diagnostic tools, and investigation of hybrids of the various techniques. The electrospun hybrid bio nanofibers are generally limited to enhanced properties of immunogenicity, cell adhesion to differentiation, neovascularization and tissue securement, flexibility, conductivity, and strain-stiffening. Sustained loading and release of bioagents due to the large surface area created *via* the exploited techniques of blend, emulsion, coaxial, and microsol electrospinning for enhanced therapy, is the other achievement attained with electrospun hybrids. Nevertheless, various impediments consisting of insufficient optimization and agglomeration have led to a persistently low mechanical strength. Also, the employed organic solvents have continuously caused inactivation and denaturation of proteins, and aggregation. The use of high-speed rotating collectors and the precise control of the electrical and magnetic fields have lessened the formation of random and dense aggregates. Untimely drug release is a primary obstacle that should not be sacrificed by the researchers.

The prospect of spun nanofibers with a focus on intelligent biomaterials

The world has liberally debated the primitively fabricated materials amidst the demand for advanced biomaterials, probably due to the costly evolution and thus limited technology. Advanced biomaterials are those classified for use in smart and intelligent biosystems. The two terms (smart and intelligent) are unfairly described and used commutatively when referring to advanced materials, but amidst, a diverse difference exists. Kai and group [10] recently attempted to freshly redefine intelligent materials with a new perspective involving their comparison to human neural networks and as materials that are capable of sensing stimuli and then learn, comprehend complex situations, optimize response behaviors, decide, and adapt, before making purposeful executions during applications (Figure 2). Smart materials, alternatively, are limited to high sensitivity to external signals of extremely low intensity including physical, chemical, biological, or other environmental changes owed to their explicit and adaptive architectural designs. Single or dual or even multiple stimulation of smart materials then influences an intermittently controlled release of encapsulated drugs and cells *via* self-folding and self-unfolding in an 'on-off' switch, or even orientation into hierarchical structures for a directed therapy. Intelligent biomaterials within the frame of the definition of intelligence [10,11] ought to perform beyond an 'on-off' switch, to monitoring changes, learning situations, and predicting the coming scenarios while inside organisms under treatment (Figure 3). However, they are yet to be realized to this date, due to numerous known and unknown reasons.

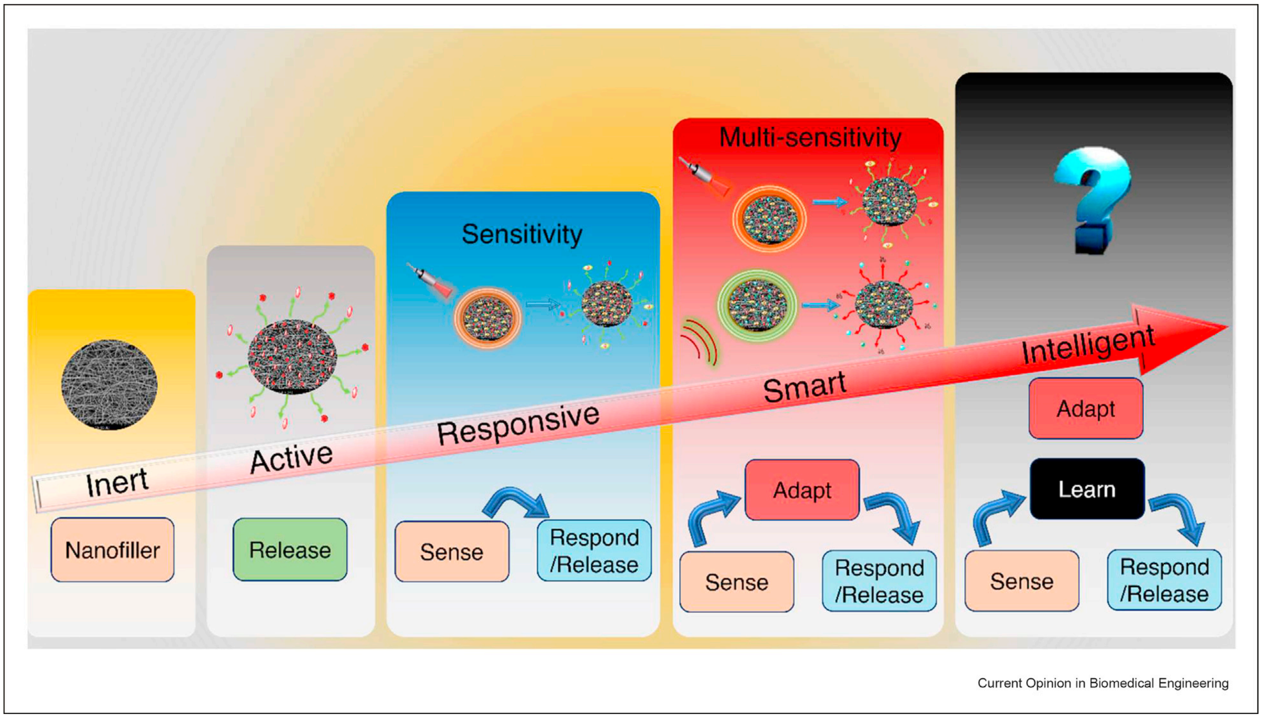
The evolution of intelligent behaviors especially in nanofibers is not a straightforward expectation since traditional electrospinning techniques are still singly employed. And for advanced functions, *in-situ* and *ex-situ* fiber modifications are required, probably coupled with other materials synthesis techniques. In connection, the fabrication of smart systems *via* additive manufacturing has allowed the introduction of printed constructs that meticulously reciprocate natural cells and tissues in terms of change in morphology and functioning after stimulation. Though smart constructs have not been perfected to function like intelligent biosystems, the 4D bio prints have enabled active adjustment among biomaterials for immediate response to the microenvironment changes [12]. 4D bioprinting is rather a newly improved technology from 3D bioprinting, involving designing programmable stimuli-responsive and precise animated multi-material biostructures including hydrogels, polymer composites,

Figure 2



Ideality of intelligent bio nanofibers.

Figure 3



Evolutionary evaluation of electrospun biomaterial, involving the inert biocompatible nanofillers, the active one-way releasers, the responsive sensors and releasers, the smart multisensors/adapters and responders, and the futuristic intelligent biomaterials.

elastomers, and scaffolds with reversible or irreversible transformation proficiency in conformation, properties, and function over time as the fourth dimension. The technology is also predictable and printer-independent, thus enabling self-assembly, multi-functioning, and self-repairment. 4D bioprinting allows the use of mathematical modeling to fabricate individualized shapes and sizes of biomaterials with meticulous and exceptionally oriented nano-/micro-structures that precisely mimic the morphologies and properties necessary for the replication of biological cells and tissues. This advancement arose after an inspiration from the dynamic human tissues like the continuously rhythmic heart, and the randomly contracting musculoskeletal and cardiac muscles that necessitate intelligent repair along functioning.

In the above regard, to fabricate advanced systems with special applications, electrospinning can be combined with various additive manufacturing methods including the discussed 4D bioprinting, electronic beam melting, and robocasting. Electron beam melting allows a less-costly and time-saving bottom-up electronic engineering of highly precise and densely layered metal designs with desired shapes and controlled mechanical and chemical properties. This occurs by scanning a powerfully focused electron beam to selectively melt and bond atmospherically reactive powders of metals and alloys, using data from a 3D computer-aided design (CAD) model to obtain prototype conductive biomedical implants. Robocasting ("direct ink writing") on the other hand, allows computerized engineering of pseudoplastic slurries such as ceramics *via* controlled rheology of solutions, for continuous buildup of partially dry layers, to form bio-inspired and well-designed internal and external architecture of hybrid bio prints with an excellent mechanical quality. For intelligent precision medicines, these manufacturing tools allow tailoring of biomedical clinical diagnostics and therapies such as soft autonomous biorobots, actuators, and biosensors with flexible and thus communal properties to several patients. Furthermore, smart biomaterials with morphing features have been designed in form of hydrogels, nanomaterials, and bioconjugates through numerous methods including electrospinning. These imparted features present a benefit of both spatial and temporal monitoring of stimuli for precise control in accordance with the required cellular response. For the attainment of intelligence, therefore, *ex-situ* living cells and artificial intelligent matter can be grown on these prepared nanofiber substrates to supplement adaptation and learning during the smart analysis of materials. For the prompt realization of intelligent bio nanofibers, smart processing technologies such as tri-axial electrospinning that possesses the potential of drug depot formation, among other methods can be interesting and viable.

Intelligence necessitates knowledge retention, and some characters have been portrayed among the autonomous smart materials of shape-memory electrospun fibers. This is causally evidenced by the stimuli-responsive biopolymers or the dispersed memory micro-inclusions that can attain numerous morphologies repetitively, revert to the fundamental shape and enable remote actuation control. Shape-memory bio nanofibers have been designed as luminescent medical devices and drugs, and stem cell nanocarriers. However, the polymer transformations *via* martensite nucleation are nonintelligent portraits since preprogrammed shapes are strictly restricted. The nanofibers also suffer from unanticipated fatigue and imperfect recovery. But, the employment of synthetic gene circuits [13] has proved long-term and stable memory-based functioning and trait supplementation in organisms.

Furthermore, the rise of immunomodulatory biosystems awakened the inexistence of intelligent biomaterials and has thus strongly reserved a linkage between the two terms. Some authors [14] identify these biosystems as the more adaptive/smarter or the next generation smarter biomaterials with a therapeutic memory. This is due to their successful manipulation of the host immune system, by creating a promoted and regulated setting in which local and systemic therapy is realized. Similar to the traditionally smart biomaterials, immunomodulatory biosystems are fashioned from one or more moieties. Therefore, self-replicators and learnable matter [15] are keys to realizing intelligent electrospun biomaterials for the attainment of body-induced immunity. Additionally, the modern designing and modification techniques such as 'living' and radical polymerization, and protein engineering can tolerate the controlled addition of numerous functional moieties. These moieties act as protein-reactive initiators for faster and simplified coupling to proteins, and synthesis of well-defined unnatural bio-agents such as the manmade amino acids-constituted proteins and artificial cells. Therefore, the reenactment of such developments is among the revelations of intelligent biosystems.

From sub-nano to macroscale, physiomechano properties are the spine for continuous development of electrospinning technique to fabricate nanofibers with the potential of preserving cellular activity (such as simple adhesion, duro-/topo-/chemo-taxis, matrix deposition, and remodeling) and subsequently allowing differentiation in tissues and organs. The vie to land intelligent systems should therefore account for the precise mechano-designer estimations, given the great pascal-gigapascal disparity of the body cogs. Noticeably, the elastic moduli range from 11 Pa (soft intestinal mucus) to 20 GPa (stiff cortical bone) [16]. Mimicry of the electrospun systems to the extracellular matrix dynamics in reference to the viscoelasticity, crystallinity, and other cell activities, should thus be an immense concern. The progression of this aspiration ought to amalgamate advanced approaches like; laser-perforation for regulation of the required hole sizes and space in electrospun constructs, additive manufacturing and hydrogel printing for attainment of accurate shapes and regulation of mimicry to living shapes, designing biomimetic cues for phenotypic preservation of various cells. Other relevant approaches may include high-throughput experimentation to elucidate the cell—material interaction and drug screening by analyzing nanofiber properties, artificial intelligence (including machine learning algorithms and robotics), and computational modeling for controlled theoretical experimentation of simulated electrospun designs. Also, precision to tissue mechano-adjustments is vital to evade ailments due to over or underperformance of engineered designs. Therefore, successful integration of biocompatible intelligent (sensory/learnable/memory/transducer) moieties in a single electrospun system to powerfully mimic and control the human antibodies and/or tissue anisotropy by systematically treating ailments at all pathological levels in inconstant microenvironments or stimulants, is deemed as the dawn of intelligent biomaterials.

In brief, ideal intelligent bio nanofibers are those with self-awareness and the capability to learn, notice, analyze, problem-solve, understand, and offer improvement, among other characteristics, as naturally presented in cells, animals, and humans. Therefore, the structure and functioning of cells, tissues, and organs, and the pathophysiology/mechanisms of disease invasion and metastasis are strongly decisive in designing intelligent biosystems that unequivocally replicate the human body physiology *via* precise cell—biomaterial interactions. Artificially, man has so far elaborated this intelligence in computers, mobiles, and robots. It is therefore opportune to drive the technology to biomaterials especially starting with electrospinning as the material fabrication platform courtesy of its flexibility, onto which intelligent nanomaterials and biosystems could be built. These intelligent nanofibers should act beyond detection and response, but similarly experience and symbiotically accommodate living cell activities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Ramakrishna S, *et al.*: **Electrospun nanofibers: solving global issues**. *Mater Today* 2006, **9**:40–50.

2. Lugoloobi I, *et al.*: **Cellulose nanocrystals in cancer diagnostics and treatment**. *J Contr Release* 2021, **336**:207–232.

3. * Tebyetekerwa M, Ramakrishna S: **What is next for electrospinning?** *Matter* 2020, **2**:279–283.
Describes the advanced and future possibiilities of electrospinning technique and electrospun nanofibers

4. * Al-Dhahebi AM, *et al.*: **Electrospinning research and products: the road and the way forward**. *Appl Phys Rev* 2022, **9**, 011319.
Recent comprehesive review describing electrospinning technique and its applications

5. Kai D, Liow SS, Loh XJ: **Biodegradable polymers for electrospinning: towards biomedical applications**. *Mater Sci Eng C* 2014, **45**:659–670.

6. Wu S, *et al.*: **State-of-the-art review of advanced electrospun nanofiber yarn-based textiles for biomedical applications**. *Appl Mater Today* 2022, **27**, 101473.

7. Agarwal S, Wendorff JH, Greiner A: **Use of electrospinning technique for biomedical applications**. *Polymer* 2008, **49**:5603–5621.

8. Stojanov S, Berlec A: **Electrospun nanofibers as carriers of microorganisms, stem cells, proteins, and nucleic acids in therapeutic and other applications**. *Front Bioeng Biotechnol* 2020, **8**:130.

9. Bhardwaj N, Kundu SC: **Electrospinning: a fascinating fiber fabrication technique**. *Biotechnol Adv* 2010, **28**:325–347.

10. Liu K, *et al.*: *Intelligent materials.* Matter; 2020.
Describes what intelligence should be in materials

11. Hanselka H, Nuffer J: **Intelligent materials**. In *Technology guide.* Springer; 2009:48–51.

12. ** Amukarimi S, Ramakrishna S, Mozafari M: **Smart biomaterials—a proposed definition and overview of the field**. *Current Opinion in Biomedical Engineering* 2021, **19**, 100311.
Proposes new and better definition of smart biomaterials

13. Lloyd JPB, *et al.*: **Synthetic memory circuits for stable cell reprogramming in plants**. *Nat Biotechnol* 2022. https://doi.org/10.1038/s41587-022-01383-2.

14. Montoya C, *et al.*: **On the road to smart biomaterials for bone research: definitions, concepts, advances, and outlook**. *Bone Res* 2021, **9**:12.

15. ** Kaspar C, *et al.*: **The rise of intelligent matter**. *Nature* 2021, **594**:345–355.
Reviews the progress towards implementations of intelligent matter using molecular systems, soft materials or solid-state materials

16. Guimarães CF, *et al.*: **The stiffness of living tissues and its implications for tissue engineering**. *Nat Rev Mater* 2020, **5**:351–370.